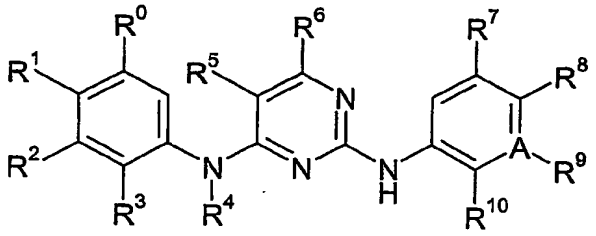
Claims

1. A compound of formula I



(I)

wherein

each of R^0, R^1, R^2,and R^3 independently is hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro; or

R^0 and R^1, R^1 and R^2, and/or R^2 and R^3 form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

R^4 is hydrogen or C_1-C_8alkyl;

each of R^5 and R^6 independently is hydrogen, C_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, cyano, or nitro; and

each of R^7, R^8, R^9, and R^{10} independently is C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-

C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro; wherein R^7, R^8 and R^9 independently of each other can also be hydrogen;

or R^7 and R^8, R^8 and R^9, and/or R^9 and R^{10} form together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

A is C or N;

and salts thereof.

2. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^1 is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^3 is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, C_1-C_8alkoxy, substituted amino, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, substituted or unsubstituted carbamoyl, unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 is $-CH_2-NH-CO-$, $-CH_2-CH_2-NH-CO-$, $-CH_2-CO-NH-$, $-CH_2-CH_2-CO-NH-$, $-CH_2-NH-SO_2-$, $-CH_2-CH_2-NH-SO_2-$, $-CH_2-SO_2-NH-$, $-CH_2-CH_2-SO_2-NH-$, $-CH_2-CH_2-SO_2-$, $-CH_2-CH_2-CH_2-SO_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl;

R^4 is hydrogen or C_1-C_8alkyl;

R^5 is hydrogen; C_1-C_8alkyl, halogen, haloC_1-C_8alkyl, cyano or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, C_1-C_8alkylsulfonyl, halogen, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano, or nitro; and

R^{10} is C_1-C_8alkyl, hydroxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, is –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -CH_2-CH_2-O-, -CH=CH-O-, -O-CH_2-O-, or -O-CF_2-O-;

A is C or N.

3. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, or halogen;

R^1 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen;

R^3 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, C_1-C_8alkoxy,

substituted amino, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, substituted or unsubstituted carbamoyl, or unsubstituted or substituted sulfamoyl; or

each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 is $-CH_2-NH-CO-$, $-CH_2-NH-SO_2-$, $-CH_2-CH_2-SO_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl;

R^4 is hydrogen;

R^5 is hydrogen, halogen, haloC_1-C_8alkyl, or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted sulfamoyl, or nitro; and

R^{10} is C_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, or halogen; or

each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, is –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$;

A is C or N.

4. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy;

R^1 is hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl; or

the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 is $-O-CH_2-O-$, or the pair of adjacent substituents R^2 and R^3 is $-CH_2-NH-CO-$ or $-CH_2-NH-SO_2-$;

R^4 is hydrogen;

R^5 is hydrogen, chloro, bromo, trifluoromethyl or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

R^8 is hydrogen, C_1-C_8alkyl, haloC_1-C_8alkyl, C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, C_1-C_8alkoxy, haloC_1-C_8alkoxy, C_5-C_{10}aryloxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted sulfamoyl, or nitro; and

R^{10} is C_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstituted or substituted amino, or halogen; or

each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, is –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-CH_2-CH_2-, -O-CH_2-O-, or -O-CF_2-O-;

A is C or N.

5. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy;

R^1 is hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl; or

the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 is -O-CH_2-O-, or the pair of adjacent substituents R^2 and R^3 is -CH_2-NH-CO- or -CH_2-NH-SO_2-;

R^4 is hydrogen;

R^5 is hydrogen, chloro, bromo, trifluoromethyl or nitro;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy,

ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

R^8 is hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro; and

R^{10} is methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; or

the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 is $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} is -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$;

A is C or N.

6. A compound of formula I according to claim 1, wherein

each of R^0, R^1 or R^2 is hydrogen;

R^3 is sulfamoyl, methylsulfamoyl or propylsulfamoyl;

R^4 is hydrogen;

R^5 is chloro or bromo;

R^6 is hydrogen;

each of R^7 and R^9 independently is hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

R^8 is hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro; and

R^{10} is methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; or

the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 is $-O-CH_2-O-$, or the pair of adjacent substituents R^9 and R^{10} is -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$;

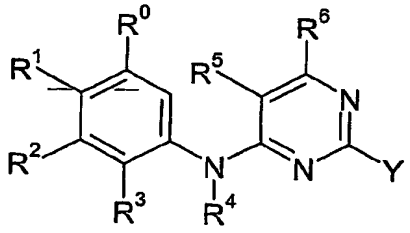
A is C or N.

7. The compound of formula I according to claim 1, wherein each of R^0, R^1 or R^2 is hydrogen, R^3 is methylsulfamoyl, R^4 is hydrogen, R^5 is bromo, R^6 is hydrogen, each of R^7 and R^8 is methoxy, R^9 is hydrogen, and R^{10} is methyl, and A is C or N.

8. The compound of formula I according to claim 1, wherein each of R^0, R^1 or R^2 is hydrogen, R^3 is methylsulfamoyl, R^4 is hydrogen, R^5 is bromo, R^6 is hydrogen, each of R^7 and R^8 is hydrogen, and the pair of adjacent substituents R^9 and R^{10} is $-CH_2-CH_2-CH_2-$, and A is C or N.

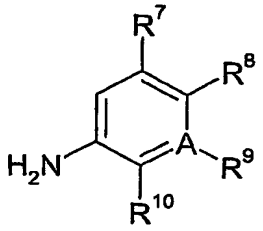
9. The compound of formula 2-{5-Chloro-2-[4-(3-methylamino-pyrrolidin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-isopropyl-benzenesulfonamide.

10. A process for the production of a compound of formula I according to claim 1, comprising reacting a compound of formula II



(II)

wherein R^0, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in claim 1, and Y is a leaving group, with a compound of formula III



(III)

wherein R^7, R^8, R^9 and R^{10} are as defined in claim 1;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined in claim 1, into another compound of formula I as defined in claim 1;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, as active ingredient together with one or more pharmaceutically acceptable diluents or carriers.

12. The use of a compound according to any one of claims 1 to 9 for the manufacture of a medicament for the treatment or prevention of neoplastic diseases and immune system disorders.

13. A combination comprising a therapeutically effective amount a compound according to any one of claims 1 to 9 and one or more further drug substances, said further drug substance being useful in the treatment of neoplastic diseases or immune system disorders.

14. A method for the treatment of neoplastic diseases and immune system disorders in a subject in need thereof which comprises administering an effective amount of a compound according to any one of claims 1 to 9 or a pharmaceutical composition comprising same.

15. Use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of a disease which responds to inhibition of focal adhesion kinase or/and IGF-1 Receptor.

16. The use according to claim 15, wherein the disease to be treated is selected from proliferative disease .

17. The use according to claim 16, wherein the proliferative disease to be treated is selected from a tumor of, breast, renal , prostate, colorectal, thyroid, ovarian, pancreas, neuronal, lung, uterine and gastro-intestinal tumours as well as osteosarcomas and melanomas.

18. The use according to claim 15, wherein the disease to be treated is an immune disease.

19. Use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment or prevention of inflammatory and/or an immune disorder.

20. Use according to claim 19 wherein the inflammatory and/or immune disorder is selected from transplant rejection, allergy and autoimmune disorders mediated by immune cells including T lymphocytes, B lymphocytes, macrophages, dendritic cells, mast cells and eosinophils.

21. The use according to any one of claims 14 to 19, wherein the compound is 2-[5-Bromo-2-(2-methoxy-5-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide or a pharmaceutically acceptable salt thereof.

22. The use according to any one of claims 14 to 19, wherein the compound is selected from 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide, N^2-(4-[1,4']Bipiperidinyl-1'-yl-2-methoxy-phenyl)-5-chloro-N^4-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine and 2-{5-Chloro-2-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-isopropyl-benzenesulfonamide, or a pharmaceutically acceptable salt thereof.